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Abstract: Background: The use of probiotics as prophylaxis for necrotizing enterocolitis (NEC) in preterm infants is being increasingly practised. Objective: We report, for the first time, a case series of 3 preterm, very-low-birth-weight (VLBW) infants who developed bacteremia with Bifidobacterium longum on probiotic therapy with Infloran® containing viable B. longum. Methods: We retrospectively reviewed data of 3 infants (of gestational age <30 weeks and birth weight <1,230 g). They were admitted to the neonatal intensive care unit. Clinical data were retrieved from their medical records. Results: In infants 1 and 2, B. longum was isolated from the blood cultures when they were on probiotic therapy with Infloran or shortly after, respectively, and was interpreted as transient bacteremia. The clinical presentation of these infants did not require antibiotic treatment after the isolation of B. longum. Infant 3 developed an NEC despite probiotic therapy with Infloran and the blood cultures showed B. longum growth. This infant required explorative laparotomy and antibiotic treatment. The clinical isolates of B. longum and the strain of the Infloran capsule showed an identical profile on biochemical, mass-spectrometric and molecular analyses, suggesting a direct correlation between the administration of probiotics and bacteremia with B. longum in all 3 infants. Conclusions: The occurrence of bacteremia with bifidobacteria after its prophylactic administration in VLBW infants and its possible clinical consequences are a matter of concern. In the interests of safety, the use of probiotics in such a population should be indicated with caution and requires further investigation.

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Case Series of *Bifidobacterium longum* Bacteremia in Three Preterm Infants on Probiotic Therapy

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Key Words
Probiotics · *Bifidobacterium longum* · Preterm infants · Bacteremia · Necrotizing enterocolitis

Abstract
Background: The use of probiotics as prophylaxis for necrotizing enterocolitis (NEC) in preterm infants is being increasingly practised. ***Objective:*** We report, for the first time, a case series of 3 preterm, very-low-birth-weight (VLBW) infants who developed bacteremia with *Bifidobacterium longum* on probiotic therapy with Infloran® containing viable *B. longum*. ***Methods:*** We retrospectively reviewed data of 3 infants (of gestational age <30 weeks and birth weight <1,230 g). They were admitted to the neonatal intensive care unit. Clinical data were retrieved from their medical records. ***Results:*** In infants 1 and 2, *B. longum* was isolated from the blood cultures when they were on probiotic therapy with Infloran or shortly after, respectively, and was interpreted as transient bacteremia. The clinical presentation of these infants did not require antibiotic treatment after the isolation of *B. longum*. Infant 3 developed an NEC despite probiotic therapy with Infloran and the blood cultures showed *B. longum* growth. This infant required explorative laparotomy and antibiotic treatment. The clinical isolates of *B. longum* and the strain of the Infloran capsule showed an identical profile on biochemical, mass-spectrometric and molecular analyses, suggesting a direct correlation between the administration of probiotics and bacteremia with *B. longum* in all 3 infants. ***Conclusions:*** The occurrence of bacteremia with bifidobacteria after its prophylactic administration in VLBW infants and its possible clinical consequences are a matter of concern. In the interests of safety, the use of probiotics in such a population should be indicated with caution and requires further investigation.

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Introduction

Necrotizing enterocolitis (NEC) is one of the major causes of neonatal mortality (at least 20–30%) and morbidity in very-low-birth-weight (VLBW) infants, defined as infants with a birth weight <1,500 g [1]. Different factors are responsible for the development of NEC. In premature infants, colonization of the gut with probiotic organisms such as bifidobacteria and lactobacilli is poor and often delayed; there may be a shift to potentially pathogenic bacteria due to delivery by cesarean section, delayed breastfeeding or empirical antibiotic treatment after birth [2]. In recent decades, administration of probiotics con-

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taining viable microorganisms was introduced. Probiotics are thought to promote the colonization of the gut with beneficial microbial flora, prevent the colonization of pathogens, improve the maturity and function of the gut mucosal barrier and modulate the immune system [2]. Based on these properties, probiotics are being increasingly used to prevent NEC in VLBW infants and have been shown to reduce both the incidence and the all-cause mortality of NEC [3].

In our clinical care, since 2007, the probiotic Infloran® is given to all preterm (gestational age <32 weeks) and/or VLBW infants. Usually, probiotics are given for a duration of 2 weeks, starting from the first day of life in infants not on antibiotics or after antibiotic treatment has been discontinued. Up to now, treatment with probiotics has appeared to be safe. However, isolated cases of probiotic sepsis in infants in neonatal intensive care units have been reported [4, 5]. We present, for the first time, a case series of 3 premature infants, who developed a *Bidifobacterium longum* bacteremia under therapy with a probiotic (Infloran; Desma Healthcare SpA, Torino, Italy) containing viable *B. longum* and *Lactobacillus acidophilus* administered for the prevention of NEC.

Methods

This is a retrospective case description of 3 infants admitted to the neonatal intensive care unit between July and December 2012 at the University Hospital of Zurich, Zurich, Switzerland. Clinical data were retrieved from the patients' medical records. A written informed consent was obtained from the parents.

Microbiological analyses were performed as follows. Blood cultures (BacT/ALERT FA aerobic®, bioMérieux, Marcy-l'Etoile, France) were aerobically incubated at 37°C for 6 days. Bacterial strains were identified by conventional biochemical methods, matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) with the MALDI Biotyper software package (version 3.0) with reference database V.3.1.2.0 (Bruker Daltonik GmbH, Bremen, Germany) and by molecular analyses of partial 16S rRNA gene [6]. An 800-bp 16S rRNA gene fragment including conserved and hypervariable regions was sequenced. Antibiotic susceptibility testing was performed with Etest strips (AB bioMérieux).

Results

Clinical Course

Patient 1

A preterm girl presented with mild respiratory distress and required respiratory assistance during the first 9 days of life (table 1). A hemodynamically nonsignificant persistent ductus arteriosus closed under treatment with indomethacin (dosage 0.1 mg/kg/day on days 3–8). On day 1, enteral feeding was started as well as Infloran administration (fig. 1). On day 6, she developed apneic episodes, suggesting a nosocomial infection. Antibiotic treatment with flucloxacillin and gentamicin was initiated empirically and stopped after 48 h as the blood cultures remained negative (fig. 1). On day 13, the baby developed local periumbilical redness with a small amount of pus. Flucloxacillin and gentamicin were instituted empirically. *Staphylococcus aureus* was cultured from the umbilical pus, but the blood cultures remained negative. On day 20, the girl presented with marbled, pale skin and a slightly distended abdomen. Antibiotic treatment was continued for 48 h. A cerebrospinal fluid evaluation was negative; however, in the blood cultures obtained on day 20, *B. longum* growth was observed on day 23. The baby improved and blood cultures taken on day 27 remained negative. She displayed a complicated clinical course with sequential antibiotic therapy, so the probiotic Infloran was continuously administered from birth to day 28. The baby was discharged home without further complications.

Patient 2

A preterm boy was intubated and given surfactant 10 min after birth. His respiratory course was complicated with 3 episodes of mechanical ventilation during the first month, supplemental oxygen up to day 63 and the development of moderate bronchopulmonary dysplasia (table 1). Amoxicillin and gentamicin were started empirically at birth and stopped after 48 h as the blood cultures were negative and the baby had no signs of sepsis (fig. 1). Enteral feeding was started on day 1 (table 1). From day 3, the probiotic Infloran was administered for the prevention of NEC and discontinued on day 17. Nosocomial infection was suspected on day 20 and therefore the central line was removed. Blood cultures were taken and empirical antibiotic treatment with amoxicillin and gentamicin was initiated for 48 h. On day 23, the blood cultures taken on day 20 displayed *B. longum* growth but the baby was stable. The boy remained asymptomatic and was discharged home without needing supplemental oxygen.

Patient 3

A preterm girl had an uncomplicated adaptation after the application of nasal continuous positive airway pressure for the first 2 days (table 1). From the first day of life, enteral feeding and administration of the probiotic Infloran were initiated (fig. 1). On day 11, she suddenly dete-

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Table 1. Demographic data of 3 patients

	Patient 1	Patient 2	Patient 3
Gestational age, weeks	30	28	29
Birth weight, g	1,200	850	1,230
Birth mode	Cesarean section	Cesarean section	Cesarean section
Reason for prematurity	Maternal preeclampsia	Premature prolonged rupture of membranes for 6 days, chorioamnionitis (confirmed on histology)	Chorioamnionitis (confirmed on histology)
Apgar score at 1, 5 and 10 min	8, 9, 8	2, 5, 5	6, 6, 7
Enteral feeding	Breast and formula milk (Prematil HA®); parenteral feeding	Breast and formula milk (Prematil HA®)	Breast and formula milk (Prematil HA®)
Respiratory assistance	Supplemental oxygen, nCPAP	Mechanical ventilation, surfactant, supplemental oxygen	nCPAP
Other management	Indomethacin for persistence of ductus arteriosus	–	Bowel resection due to short bowel syndrome
Outcome	Discharge at gestational age 36 weeks and body weight 2,030 g	Discharge at gestational age 39 weeks and body weight 2,890 g	Discharge after 11 months and with a body weight of 9,895 g, with parenteral nutrition

nCPAP = Nasal continuous positive airway pressure.

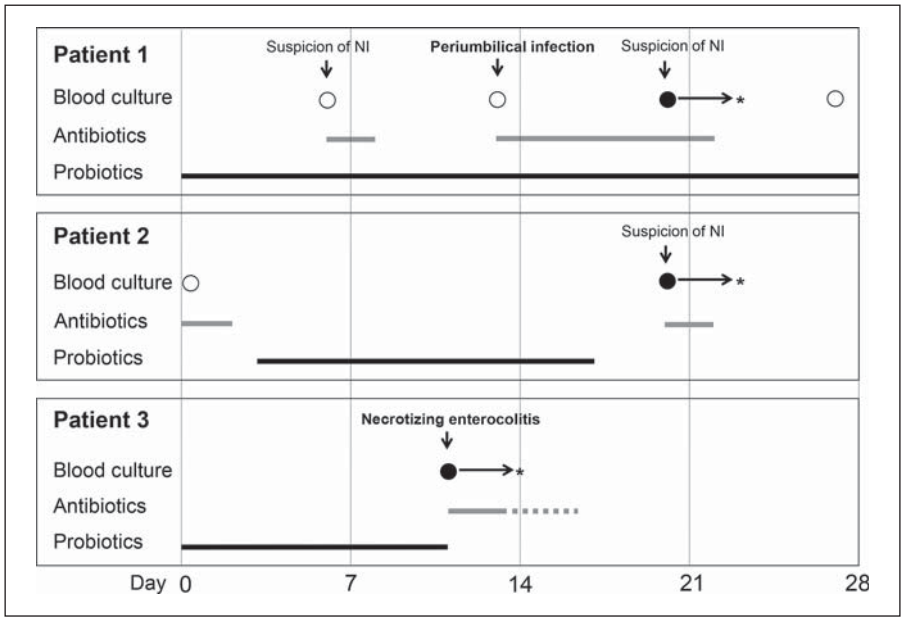

Fig. 1. Clinical courses of 3 preterm infants with *B. longum* bacteremia. Illustration of the blood culture results in relation to the administration of probiotics (containing *B. longum*) and antibiotics to 3 preterm infants with bacteremia due to *B. longum*. ○ = Negative blood cultures. ● = Positive blood cultures. The asterisk marks the isolation of *B. longum*. Empirical antibiotic treatment consisted of flucloxacillin and gentamicin on days 6–8 and 13–22 in patient 1, amoxicillin and gentamicin on days 1–3 and 20–22 in patient 2 and amoxicillin clavulanic acid and gentamicin from day 11 in patient 3. NI = Nosocomial infection.

riorated, with clinical signs of acute NEC confirmed by pneumatosis on X-ray. Amoxicillin clavulanic acid and gentamicin were started empirically; enteral feeding and probiotics were discontinued. Explorative laparotomy was undertaken which confirmed the diagnosis of extended NEC stage III (according to the modified Bell staging criteria [7]). Resection of 23 cm of small bowel was performed on day 11. On day 14, growth of *B. longum* was detected in the blood cultures taken on day 11. The baby had a complicated postoperative course with serial laparatomy, parenteral nutrition and delayed enteral feeding.

Microbiological Analyses

For comparison, the Infloran capsule was inoculated on Brucella agar. *Bifidobacterium* spp. were identified from the blood and the Infloran capsule based on typical pleomorphic Gram staining and biochemical reactions (acidification of glucose, saccharose, maltose and fruc-

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tose but no acidification of xylose and mannose). Analysis of all isolates by MALDI-TOF MS revealed identification as *B. longum* with a score of >2.0, which allows for species assignment. The bifidobacteria isolates derived from the clinical samples and the Infloran capsule had a 100% 16S rRNA gene sequence similarity. Antibiotic susceptibility testing revealed a minimal inhibitory concentration of 0.094 mg/l for penicillin.

Discussion

To our knowledge, this is the first report of a case series of the development of bacteremia in VLBW infants that can be attributed to the probiotic strain *B. longum*. For patients 1 and 2, the positive blood cultures with *B. longum* were interpreted as transient bacteremia rather than septicemia. For patient 3, we have to speculate whether the *B. longum* bacteremia was the consequence or the cause of the NEC with perioperative hematogenous dissemination of the bacteria. Nevertheless, the bifidobacteria obtained from the patient samples and the Infloran capsule displayed an identical genetic and biochemical profile, suggesting a direct correlation between the administration of probiotics and bacteremia in all 3 VLBW infants.

In a very recent Cochrane report including randomized controlled trials, the evidence for probiotics in preventing NEC and all-cause mortality in preterm infants was strongly supported and implied a change in practice [3]. Moreover, Härtel et al. [8] demonstrated the benefit of probiotics in the VLBW infant population for reducing the gastrointestinal morbidity. In both studies, no probiotic systemic infections were observed; however, in the absence of clinical signs, an asymptomatic transient bacteremia with probiotic microorganisms could have been missed. Despite the strong evidence for the use of probiotics in preterm infants, there are concerns regarding its safety. The risk of bacterial transformation and possible infection by probiotic strains has to be examined [9]. For safety reasons, both the European and the American Committees on Nutrition [2, 9] have underlined the need for large, well-designed multicenter trials before the widespread use of probiotics in VLBW infants can be recommended.

The occurrence of sepsis due to probiotics is not a novelty; there are reports of sepsis due to lactobacilli in groups of pediatric and adult patients [10]. Over a 5-year period with a total of 681 blood cultures obtained from neonates at our hospital, we detected *B. longum* bacteremia only in the 3 (0.4%) cases reported here. The blood culture systems used nowadays largely allow for accurate detection of this fastidious Gram-positive rod, so an underestimation seems unlikely. We are not able to conclude whether the probiotic strain *B. longum* was associated only with bacteremia or indeed caused an infection with NEC in patient 3. Nevertheless, our data documenting probiotic bacteremia in preterm neonates necessitate caution with the use of probiotics in this vulnerable population.

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